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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,070	10/30/2003	Frederic J. Kaye	221749	1623

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,070	KAYE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *7,17 and 27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-15 and 18-26* is/are rejected.

7)☒ Claim(s) *6 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

In the restriction requirement mailed May 2, 2005, the paragraph indicating that the independent sequence inventions are linked was inadvertently omitted. This paragraph is included below.

1. Claim 1 link(s) the inventions of claims 6, 7, 16 and 17. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

1. Applicant's election with traverse of group I, claims 1-26 and SEQ ID NO: 5 in the reply filed on June 6, 2005 is acknowledged. The traversal is on the ground(s) that there would not be a serious burden in examining inventions I and II together because

any search of the subject matter of group I would necessarily overlap with the subject matter of group II. This is not found persuasive because in order to search for prior art that may anticipate or render obvious a composition it is not necessary to thoroughly search each individual step of a method. Thus, while the search of a composition may overlap with a search of a method of using that composition, the searches do not overlap fully, they are not coextensive. Therefore a serious burden would exist in examination of both of inventions I and II.

Applicant also traverses the restriction requirement between sequences and refers to this requirement as a provisional restriction. Notwithstanding the presence of a linking claim, a restriction between sequences is in no way a provisional restriction but is a restriction between independent and distinct inventions. The traversal is on the grounds that there would not be an undue burden on the Examiner in examining other sequences. Applicant's arguments pointing out that SEQ ID NO: 2 is fully encompassed within SEQ ID NO: 5 is persuasive and these sequences are rejoined. However, these arguments are not persuasive with regard to SEQ ID NOS: 8 and 9 being near complements of SEQ ID NO: 5. It is noted that a search of the available sequence databases produces a listing of references disclosing the sequence most similar to the query sequence. This is the "place" where the examiner searches for prior art and for SEQ ID NO: 5 this will be uncovered in a search of the larger sequence of SEQ ID NO: 2. The prior art relating to another query sequence such as SEQ ID NOS: 8 and 9 will not be found in this "place"- a different listing of references must be generated and searched by the examiner, producing a serious search burden in examining more than one sequence.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 7, 17 and 27-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 6, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 depends from claim 2 which depends from claim 1 and recites that the fragment of the chimeric gene and its complement are joined by a restriction enzyme sequence. Restriction enzymes are recognized by the art to cleave DNA, not join fragments. Claims 12-14 are indefinite for the same reason due to their dependence on claim 3.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 8-15 and 18-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

4. Claim 1 is directed to a composition for the inhibition of translation of a Mect1-MAML2 chimeric gene comprising a fragment of the chimeric gene and its complement. Claim 5 limits the chimeric gene to those resulting from a t(11;19) translocation. All of the other claims depend from claim 1. Claim 1 encompasses a broad genus of compounds that are compositions comprising a fragment of any Mect1-MAML2 chimeric gene from any species.

5. The specification describes a human Mect1-MAML2 chimeric gene resulting from the fusion of exon 1 of Mect1 in-frame with exons 2-5 of MAML2; the sequence of which can be found in Genbank. The specification does not describe nor is it known in the art the structure of what domains of the Mect1-MAML2 chimeric gene correspond to Mect1-MAML2 function. Mect1-MAML2 chimeric genes are not well known in the art and it not known if the function of Mect1-MAML2 is uniquely due to the particular combination of exons described in the instant specification or if other possible exon combinations exist that give rise to Mect1-MAML2 chimera having a different structure but having the identical function. Additionally, the specification describes a chimeric gene resulting from fusion of human Mect1 and MAML2 but does not describe any Mect1-MAML2 chimeric genes from any other species.

6. Without a disclosure relating the structure of Mect1-MAML2 to its function, the skilled artisan would be unable to envision the structure or structures that correspond to the function of being a Mect1-MAML2 chimeric gene. Without such knowledge, the skilled artisan would be unable to derive a composition for inhibition of the gene comprising a fragment of such a chimeric gene and its complement.

7. Therefore, while the specification provides adequate description of the Mect1-MAML2 chimeric gene shown as SEQ ID NO: 1, the full breadth of compositions for inhibiting a Mect1-MAML2 chimeric gene that are encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 18, 19, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilda et al. (Oncogene 2002, cited on IDS) in view of Tonon et al. (Nature Genetics 2003, cited on IDS).

8. Claim 1 is directed to a composition for inhibition of a Mect1-MAML2 chimeric gene that consists essentially of a fragment of the nucleotide encoding the chimeric gene and a nucleic acid complementary to the fragment wherein the fragment is 17-32 nucleotides in length. Claims 4 and 5 limit claim 1 by stating the chimeric gene has the sequence shown in SEQ ID NO: 1 and that the chimeric gene results from a t(11;19) translocation. Claims 18 and 19 limit claim 1 by stating the length of the fragment is 17-22 or 19-21 nucleotides in length. Claims 23 and 24 limit claim 1 by stating that when annealed the fragment and its complement have 3' overhangs of 1-4 or 2-3 nucleotides.

9. Wilda et al. teach that chromosomal translocations are a hallmark of several types of cancers and frequently lead to the generation of chimeric fusion oncoproteins that trigger malignant transformation and that targeting of such gene products is an ideal way to kill tumor cells specifically while leaving normal cells unaffected. Wilda et al. further teach that RNA interference enables a complete knock down of a specific protein and thus holds great therapeutic potential. Wilda et al. further teach inhibition of the BCR/ABL fusion gene through RNA interference. The siRNA used by Wilda et al. is shown in figure 1 and is a fragment of the BCR/ABL chimeric gene 19 nucleotides in

length that when annealed with its complement has 2 nucleotide overhangs at the 3' end. Wilda et al. teach on page 5722 that silencing of chimeric mRNAs may become a promising therapy. Wilda et al. do not teach compositions for inhibiting a Mect1-MAML2 chimeric gene.

10. Tonon et al. teach that mucoepidermoid cancers are characterized by a t(11;19) translocation. Tonon et al. cloned and sequenced this translocation and discovered this translocation results in a fusion of the Mect1 and MAML2 genes that disrupts a Notch signaling pathway. Tonon et al. teach the sequence of this chimeric gene is available in a public database.

11. It would have been obvious to one of ordinary skill in the art at the time of invention to make siRNAs comprising a fragment of a chimeric gene and its complement as taught by Wilda et al. to target the Mect1-MAML2 gene taught by Tonon et al. The combination of Wilda et al. and Tonon et al. provides a motivation to do so, Wilda et al. teaching that targeting of chimeric genes associated with cancer are ideal ways to target tumor cells without affecting normal cells and suggesting that RNA interference may be a promising therapy for tumor specific chimeric mRNAs and Tonon et al. teaching the sequence of a chimeric gene that is associated with mucoepidermoid cancers. One of ordinary skill in the art would have had a reasonable expectation of success in targeting Mect1-MAML2 with an siRNA because Tonon et al. provide the sequence of this chimeric gene and Wilda et al. actually make such an siRNA comprised of a fragment of a chimeric gene and its complement.

12. Thus, the invention of claims 1, 4, 5, 18, 19, 23 and 24 would have been obvious, as a whole, at the time of invention.

Claims 1, 4, 5, 8-11 and 18-24 rejected under 35 U.S.C. 103(a) as being unpatentable over Wilda et al. and Tonon et al. as applied to claims 1, 4, 5, 18, 19, 23 and 24 above, and further in view of Sui et al. (PNAS 2002, cited on IDS), Graham (US 6,573,099) and Nicklin et al. (Current Gene Therapy 2002, vol. 2, pages 273-293).

13. Claims 1, 4, 5, 18, 19, 23 and 24 are described in the previous rejection over Wilda et al. and Tonon et al. Claims 8-11 limit claim 1 by stating the composition is in a vector that may be a plasmid or a viral vector that may be an adenoviral vector. Claims 20-22 limit claim 1 by stating the fragment and complement are under control of different promoters that are RNA polymerase III (Pol III) promoters.

14. The teachings of Wilda et al. and Tonon et al. are described in the previous 103 rejection. Wilda et al. and Tonon et al. do not teach compositions directed to a Mect1-MAML2 chimeric gene in a vector.

15. Sui et al. teach DNA vectors for producing siRNA molecules suitable for use in RNA interference. These vectors are plasmids that operate under control of the U6 promoter, which is a Pol III promoter.

16. Graham teaches constructs for reducing gene expression containing multiple copies of genes under control of one or multiple promoters. Claim 4 teaches a construct containing a sense strand under control of a promoter and an antisense strand under control of a separate promoter.

17. Nicklin et al. teach that replication defective adenoviral vectors have been successfully used for gene delivery in many applications.

18. The teachings of Wilda et al. and Tonon et al. are obvious for the reasons described in the previous 103 rejection. It would have been further obvious to place a composition targeted to the Mect1-MAML2 chimeric gene into a vector that is a plasmid or a viral vector. Sui et al. provide a motivation to do so, teaching a plasmid vector system using Pol III promoters that produces siRNAs that reduce gene expression. Nicklin et al. provide a motivation to use an adenoviral vector by teaching that adenoviral vectors are widely used as gene delivery systems. Graham provides a motivation to place the fragment and its complement under control of different promoters, teaching a genetic construct useful in reducing gene expression that contains a sense strand and an antisense strand that are under control of individual promoters. One of ordinary skill in the art would have had a reasonable expectation of success in placing a composition comprising a fragment of a Mect1-MAML2 gene into a vector that is a plasmid or virus because Sui et al. teach that siRNAs suitable for RNA interference can be placed into such vectors and actually produce functional siRNAs.

19. Thus, the invention of claims 1, 4, 5, 8-11 and 18-24 would have been obvious, as a whole, at the time of invention.

Claims 1, 2, 4, 5, 15, 18, 19 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilda et al. and Tonon et al. as applied to claims 1, 4, 5, 18, 19, 23 and 24 above, and further in view of Parrish et al. (Molecular Cell 2000, vol. 6, pages 1077-1087) and Elbashir et al. (EMBO Journal 2001, vol. 20, pages 6877-6888).

20. Claim 1, 4, 5, 18, 19, 23 and 24 are described in the 103 rejection under Wilda et al. and Tonon et al. Claim 2 and 5 limit claim 1 by stating the complementary nucleic

acid contains 1-10 or 2-5 base substitutions. Claims 25 and 26 limit claim 23 by stating the overhang has one or more uridines.

21. The teachings of Wilda et al. and Tonon et al. are described in the 103 rejection over these references. Parrish et al. teach that base substitutions commonly used in nucleic acid therapeutics are tolerated in the double stranded RNAs used for RNA interference.

22. Elbashir et al. teach that siRNAs are most efficient at RNA interference when there are 2 nucleotide overhangs at the 3' end and teach on page 6884, first column that overhangs of UU or UG are 2-4 times more active than overhangs of AA, CC or GG.

23. The teachings of Wilda et al. and Tonon et al. are obvious for the reasons described above. It would have been further obvious to one of ordinary skill in the art at the time of invention to make siRNAs containing base substitutions or 2 nucleotide 3' overhangs that are UU. Parrish provides a motivation to do use base substitutions, teaching that base modifications known in the art of nucleic acid therapeutics to impart increased stability are tolerated in the double stranded RNA used in RNA interference. Elbashir et al. provides a motivation to use overhangs, teaching that 2 nucleotide overhangs of UU are more efficient mediators of RNA interference than overhangs of AA, CC or GG. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Wilda et al. and Tonon et al. of RNA interference inhibition of chimeric genes with the teachings of Parrish et al. and Elbashir et al of modifications to siRNAs because Parrish et al. and Elbashir et al. actually made

such modified double stranded RNAs and demonstrated that they work to reduce gene expression by RNA interference.

24. Thus, the invention of claims 1, 2, 4, 5, 15, 18, 19 and 23-26 would have been obvious, as a whole, at the time of invention.

Allowable Subject Matter

Claims 6 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811.

On July 15, 2005, the Central FAX Number was changed to 571-273-8300. Faxes sent to the old number (703-872-9306) will be routed to the new number until September 15, 2005.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
August 19, 2005

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PATENT EXAMINER